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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,461	12/04/2003	John D. Shaughnessy	D6485	6235

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,461	SHAUGHNESSY, JOHN D.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18,19,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *39-40* is/are allowed.

6)☒ Claim(s) *15,18 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/27/2007 has been entered.

Claims 15, 18-19 and 39-40 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of claims 15 and 18 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing a Dkk-1 associated lytic bone disease in an individual having multiple myeloma, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein, does not reasonably provide enablement for a method of diagnosing any and/or all Wnt antagonist-associated lytic bone diseases in any test individual, comprising examining the expression level of the human homologue of Dickkopf-1 (DKK-1) protein in said test individual is withdrawn in view of Applicants amendments.

The provisional rejection of claims 15 and 18-19 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 11/176,739 is withdrawn in view of Applicants filing of the Terminal Disclaimer on 8/27/2007.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 18-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing lytic bone disease in a multiple myeloma patient treatable by decreasing Dkk-1 expression at the protein level, does not reasonably provide enablement for a method of diagnosing lytic bone disease in any individual treatable by decreasing Dkk-1 expression at the nucleic acid level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would

result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of diagnosing lytic bone disease treatable by decreasing DKK-1 expression in an individual, comprising measuring the expression level of the human homologue of DicKKopf-1 (DKK-1) protein in said individual, wherein an increased expression of said protein compared to that in a healthy individual indicates that said individual has a lytic bone disease treatable by decreasing Dkk-1 expression therein. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of diagnosing lytic bone disease treatable by decreasing DKK-1 expression in an individual, comprising measuring the expression level of the human homologue of DicKKopf-1 (DKK-1) protein in said individual, wherein an increased expression of said protein compared to that in a healthy individual indicates that said individual has a lytic bone disease treatable by decreasing Dkk-1 expression therein. Thus, the claims encompass a method of diagnosing lytic bone disease treatable by decreasing DKK-1 expression at the nucleic acid level, e.g., gene therapy, or at the protein level; and further, encompass diagnosing a treatable form of lytic bone disease in any individual.

Guidance in the specification and Working Examples

The specification teaches (page 19, lines 13-20) that examples of secreted antagonists of WNT such as Frizzled (Fz)-related proteins (FRPs), Cerberus, Wnt inhibitor factory (WIF) and Dickkopf (DKK). The specification further teaches that bone disease can be treated by inhibiting the expression of a WNT antagonist, wherein the expression of these antagonist can be inhibited at the nucleic acid or protein level such as by using anti-sense oligonucleotides or anti-DKK1 antibodies (page 25, lines 7-13 and page 26, lines 5-8). For example, the specification teaches that a Dkk-1 antibody blocks the repressive activity of Dkk-1 in C2C12 cells (page 16, lines 16-18 and page 54, lines 11-18, see also the Declaration by the inventor, Dr. John Shaughnessy, which demonstrates that the application of a neutralizing antibody directed to DKK1 results in an increase in bone mineral density of non-myelomatous bones, in vivo). Moreover, the specification teaches that 174 patients with "newly" diagnosed multiple myeloma, 16 patients with monoclonal gammopathy of undetermined significance, 9 with Waldenstroms macroglobulinemia, and 45 normal persons were studied in the present invention (page 27, lines 10-16). Specifically, the specification provides (page 35, Example 8) an analysis of the results obtained from 173 patients with myeloma, wherein the DKK1 signal for patients with 1 + MRI and no x-ray lesion differ significantly compared to patients with no MRI and no x-ray lesions, but does not differ significantly compared to patients with 1 + MRI and 1 + x-ray. In addition, the specification teaches (page 9, Example 9) a correlation between global gene expression of DKK-1 and lytic bone lesions in multiple myeloma. Thus, while the specification clearly teaches a diagnosis of bone disease in a multiple myeloma patient comprising comparing the level of DKK-1 expression in an individual with multiple myeloma compared to a "normal" individual and further, that a Dkk-1 antibody inhibits Dkk-1 at the protein level, the specification appears to be silent on a correlation between DKK-1 expression and bone diseases in any and/or all individuals. Nor does the specification appear to provide any examples of a lytic bone disease treatable by decreasing Dkk-1 expression at the nucleic acid level, e.g., gene therapy. Specifically, the specification has not taught an appropriate tested dose, the amount of expression necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. As such, if there is no correlation then the examples do not constitute working examples. While it is

understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the diagnosis of a bone disease or treatment of bone disease using gene therapy, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of diagnosis and gene therapy is extremely large given the unpredictability associated with correlating the level of DKK-1 protein expression level with the ability to provide a diagnostic evaluation of a patient suspected of exhibiting a lytic bone disorder.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that one activity associated with the DKK family of proteins is the modulation, e.g., antagonism, of the activity of the Wnt family of secreted proteins. For example, McCarthy (WO 00/52047, 2000, of record), teach a method of diagnosing a disease or disorder associated with aberrant expression or activity of DKK (abstract). While McCarthy contemplates determining the risk of developing a disease associated with aberrant expression or activity of a DKK protein (page 96, lines 14-16), there does not appear to be any demonstration that the DKK family of proteins can be used to diagnose a WNT associated lytic bone disease in any and/or all individuals.

In the instant case, the specification provides neither guidance on nor exemplification of how to correlate the level of DKK-1 protein expression level with the ability to provide a diagnostic evaluation of a patient suspected of exhibiting a lytic bone disorder. Tockman et al (Cancer Res., 1992, 52:2711s-2718s, of record) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for cancer detection, the basic principles taught are clearly applicable to other disorders such as lytic bone diseases. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear

biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4).

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. For example, those of skill in the art would recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be solved before gene

therapy will be useful for more than the rare application" (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, "the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmakinetic paradigms beyond those that describe the conventional medicines in use today". Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, "...the search for such combinations is a case of trial error for a given cell type" (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy,1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, "[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results:

convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see "3. Technical hurdles to be overcome in the future", beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants argument pertaining to the previous rejection as they relate to the instant rejection. In response to this previous rejection, Applicants assert that amended independent claim 15 has been limited to diagnosing a lytic bone disease treatable by inhibiting Dkk-1 expression in an individual having multiple myeloma, wherein the specification teaches that lytic bone disease can occur prior to

formation of multiple myeloma and Dkk-1 is a molecular determinant for lytic bone disease and how to measure the same (page 3, lines 11-13 and page 5, lines 7-16). Moreover, Applicants contend that diagnosis usually does not occur in a vacuum and that, without undue experimentation, one of ordinary skill in the art would be able to identify those individuals for which a determination of Dkk-1 expression levels should be performed to diagnose a lytic bone disease which would respond to a Dkk-1 inhibitory treatment, e.g., multiple myeloma and/or osteoporosis, given the disclosure in the specification.

These arguments have been carefully considered, but are not found persuasive.

First, regarding Applicants assertions that the amendment of claim 15, the Examiner acknowledges that Applicants contend that claim 15 has been amended to include the limitation of "an individual having multiple myeloma". However, the Examiner recognizes that claim 15 does not appear to recite the limitation "an individual having multiple myeloma". Thus, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Regarding Applicants assertion that diagnosis usually does not occur in a vacuum, the Examiner agrees with Applicants position that diagnosis does not occur in a vacuum. However, the Examiner recognizes that the specification appears to have only linked increased DKK-1 protein expression in multiple myeloma patients with lytic bone lesions (Examples 8 and 9). Moreover, the specification only appears to teach inhibition of Dkk-1 at the protein level, as stated above; and therefore, is not commensurate in scope with broad scope of the claimed invention which encompasses treatable at the nucleic acid level, e.g., gene therapy, as well.

Claims 39-40 appear to be free of the prior art; and therefore, are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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BF